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Individual and Joint Effects of Early-Life Ambient $PM_{2.5}$ Exposure and Maternal Pre-Pregnancy Obesity on Childhood Overweight or Obesity

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Abstract

Background: Although previous studies suggest that exposure to traffic-related pollution during childhood increases risk of childhood overweight or obesity (COWO), the role of early-life exposure to fine particulate matter (aerodynamic diameter <2.5 micrometers, $PM_{2.5}$) and its joint effect with mother's pre-pregnancy body mass index (MPBMI) on COWO remain unclear.

Objectives: The present study was conducted to examine the individual and joint effects of ambient $PM_{2.5}$ exposures and MPBMI on the risk of COWO.

Methods: We estimated exposures to ambient $PM_{2.5}$ in utero and during the first 2 years of life (F2YL), determined with data from EPA's Air Quality System matched to residential address, in 1446 mother-infant pairs, recruited at birth from 1998 and followed-up prospectively through 2012 at the Boston Medical Center in Massachusetts. We quantified the individual and joint effects of $PM_{2.5}$ exposures with MPBMI on COWO, defined as child's age- and sex-specific BMI z-score≥85th percentile at last well-child care visit between age 2 and 9 years. Additivity was assessed by estimating reduced excess risk due to interaction.

Results: Comparing the highest and lowest quartiles of $PM_{2.5}$, the adjusted RR (95% CIs) of COWO were 1.3(1.1, 1.5), 1.2(1.0, 1.4), 1.2(1.0, 1.4), 1.3(1.1, 1.6), 1.3(1.1, 1.5) and 1.3(1.1, 1.5) during preconception, 1st, 2nd and 3rd trimester, entire period of pregnancy, and F2YL, respectively. Spline regression showed dose-response relationship between $PM_{2.5}$ levels and COWO after a threshold near the median exposure (10.46 $\mu g/m^3$ – 10.89 $\mu g/m^3$). Compared to their counterparts, children of obese mothers exposed to high $PM_{2.5}$ had the highest risk of COWO (RR≥2.0, RERI not significant).

Conclusions: In this study, we observed that early-life $PM_{2.5}$ exposures may play an important role in the early-life origins of COWO and may increase risk of COWO in children of mothers who were overweight or obese before pregnancy beyond the risk due to MPBMI alone. Our findings underscore the clinical and public health policy relevance of early-life $PM_{2.5}$ exposures.

Introduction

Prevalence of childhood overweight and obesity (COWO) has reached alarmingly high levels in the past decade, surpassing 30% in the U.S. and other developed countries (Ogden et al. 2014; WHO 2013). COWO is associated with metabolic syndrome (Weiss et al. 2004), type 2 diabetes (Goran et al. 2003), and early signs of cardiovascular disease in childhood and adolescence (Lobstein et al. 2004). Furthermore, COWO is a major risk factor for chronic diseases in adulthood including overweight and obesity (The et al. 2010), stroke (Lawlor and Leon 2005), and premature death (Franks et al. 2010). Maternal overweight and obesity at conception, which occurs in one in two mothers in the U.S.(Kim et al. 2007; Vahratian 2009), is the leading risk factor for COWO (Reilly et al. 2005), and may reflect the interaction of genetic, lifestyle, and environmental risk factors shared within families as well as prenatal programing occurring *in utero* for increased susceptibility to overweight and obesity throughout the lifespan (Gillman 2005; Janesick and Blumberg 2012; Lawlor 2013; Romano et al. 2014).

The adverse effects of air pollution *in-utero* on birth weight have been reported in multiple studies (Shah et al. 2011; Wang et al. 1997). More recently, smoking and exposure to polycyclic aromatic hydrocarbons (PAHs) during pregnancy have been linked with overweight in offspring, suggesting that the effect of early-life air pollution exposure may persist into childhood and increase risk of COWO (Oken et al. 2008; Rundle et al. 2012). Studies in the U.S. and China have shown an association between traffic-related pollution, particulate matter ≤ 10 μm in diameter (PM_{10}) exposure during childhood and increased BMI and odds of overweight or obesity in childhood or adolescence, but these studies did not include exposure during the prenatal period (Dong et al. 2014; Jerrett et al. 2010; Jerrett et al. 2014; McConnell et al. 2015). $PM_{2.5}$ during the prenatal period has also been found to be associated with rapid postnatal weight gain in infants (Fleisch et al. 2015) and similar findings have also been reported in a rodent model (Wei et al. 2016), but examination of the persistence of these prenatal effect into childhood in the current literature has been limited to one

recent study (Fleisch et al. 2016). In addition, modification of the effect of $PM_{2.5}$ by maternal overweight and obesity has not been assessed.

In this prospective cohort study, we sought to investigate the effect of early-life ambient $PM_{2.5}$ exposures on the risk of COWO, and its joint effect with maternal pre-pregnancy overweight and obesity on COWO, in the Boston Birth Cohort (BBC), a large prospective cohort of predominantly urban, low income, minority mothers and their children living in Boston, MA.

Methods

Study Population

The study population includes mother-infant pairs participating in the BBC, a prospective cohort established in 1998 at the Boston Medical Center (BMC), using a rolling enrollment. BMC serves an ethnically diverse community of patients who primarily reside in an urban setting, and the birth cohort is enriched for preterm or low birthweight birth by recruiting at a ratio of approximately 1 preterm for 2 full-term births. Multiple births and newborns with major birth defects were excluded. Detailed data collection and measurement methods for clinical and socio-demographic variables have been previously published elsewhere (Kumar et al. 2008; Wang et al. 2002). Briefly, recruitment took place 24-72 hours after birth, and informed written consent was obtained from all participating mothers. At this time, data on clinical and social variables were collected via participant interview or extraction from medical records using a structured questionnaire developed for the BBC. These data included birth weight, sex of the baby, season of delivery, maternal age at delivery, race/ethnicity, education level, smoking status before and during pregnancy, diabetes history, marital status, parity, household income, and current and previous residential addresses. Gestational age was assessed based on the date of the last menstrual period as well as results of early ultrasound (<20 weeks' gestation). Breastfeeding was assessed by a questionnaire administered during postnatal follow-up and the majority was completed before the child reached the age of 2. The study protocol

was approved by institutional review boards at the BMC and the Johns Hopkins Bloomberg School of Public Health.

Since 2003, all children enrolled in the BBC who intended to receive their primary care at the Boston Medical Center were eligible to participate in a postnatal follow-up study. Of the 2891 children followed up, 1446 were included in this analysis. As depicted in a flow chart (Figure S1), reasons for exclusion from the analysis were birth date later than November 2012 (n=84), primary care received outside BMC (n=630), $PM_{2.5}$ exposure data not available (n=438), maternal underweight (n=73), MPBMI not available (n=9) and children who have completed at least one follow-up well-child visit after 9 years old (n=211).

Assessment of Maternal and Childhood Overweight and Obesity

Children's height and weight were measured by pediatric medical staff during annual well-child care visits per clinical standard procedure and documented in the electronic medical records at the Boston Medical Center (Wang et al. at press). For children younger than 2 years old, the recumbent length was measured as the height (Rifas-Shiman et al. 2012). While for children at age 2-9, the staff measured the height standing without shoes. The weight of all children wereerewere measured on a pediatric scale. BMI was calculated as the weight divided by height squared (kilograms per meter squared). BMI-z, defined as the number of standard deviations by which a child differs from the mean BMI of children of the same age and sex, was calculated using the SAS Program for the 2000 CDC Growth Charts provided by the CDC (CDC 2011). Childhood overweight was defined as a BMI z-score $\geq 85^{th}$ percentile and $< 95^{th}$ percentile and childhood obesity as a BMI z-score $\geq$ the 95^{th} percentile. Since the length of follow-up and the number and frequency of annual well-visits varied by participant, COWO was defined as childhood overweight or obesity between ages 2 and 9 years based on the last recorded BMI-z score.

Maternal pre-pregnancy body mass index (MPBMI) was calculated as weight in kilograms divided by height in meters squared based on the mother's height and weight before pregnancy,

collected from maternal questionnaire interview and electronic medical records. MPBMI was categorized into 3 groups: BMI from 18.5 to 24.9 kg/m^2 (normal-weight), BMI from 25.0 to 29.9 kg/m^2 (overweight) and BMI≥30.0 kg/m^2 (obesity).

Ambient $PM_{2.5}$ Exposure Assessment

We assigned individual $PM_{2.5}$ exposure values to mothers (for periods of pregnancy) and children (for the first 2 years after birth) based on euclidean minimum distance from the air pollution monitoring sites to the mother's residential address, which was converted from the physical address by street level with the PROC GEOCODE statement of SAS 9.4 (SAS Institute Inc.), and matched to the nearest monitor using ArcGIS 10.2 (Esri, Inc.). We imposed no limits on the distance between participants and monitors. Only data from monitors with at least 1 measurement per week for more than 75.0% of the study period were included in the final analyses. A map of the study area depicting the locations of subjects relative to monitor locations was reported elsewhere (Nachman et al. 2016). Exposure periods were defined based on the gestational age of the infant at birth and divided into 6 phases: preconception (90 days before pregnancy), the 1st trimester (day 1 to day 90 of pregnancy), the 2nd trimester (day 91 to day 180 of pregnancy), 3rd trimester (day 181 of pregnancy to birth), whole pregnancy (day 1 of pregnancy to birth) and first 2 years of life (F2YL) (the first two years after birth). Exposure to $PM_{2.5}$ was assessed for each individual participant as the geometric mean of the daily $PM_{2.5}$ ambient concentrations during a given exposure period of interest. Daily $PM_{2.5}$ concentration data came from the monitor closest to the participant's date-specific address. If a participant moved, daily data was used from the monitor closest to the new address, starting on the date of the move. Quartiles of exposure were determined separately for each pregnancy period from the distribution of individual participant exposures during that period. The exposure was categorized by quartile and as a continuous variable for analyses of individual effects of $PM_{2.5}$ and as a dichotomous variable for the analysis of joint effects of $PM_{2.5}$ and MPBMI on COWO.

Statistical Analyses

Population characteristics between children with COWO and their controls were compared as follows. Continuous variables such as gestational age, birth weight, etc. were descripted with median (1^{st} quartile, 3^{rd} quartile), and Mann-Whitney U test was applied to compare the differences between the two groups since the distributions were skewed. Chi-square tests were used to describe and compare the differences of the proportion of categorical variables between the two groups.

We estimated the individual and joint effects of pre- or postnatal ambient $PM_{2.5}$ exposures and MPBMI on either COWO or BMI-z, using multivariable generalized linear models (GLM). Given that the outcome COWO is common, raising concerns that the odds ratio would overestimate risk and interactions, associations between the contributing variables of interest and COWO (dichotomous, where y=1 indicates COWO) were quantified by relative risk using a "modified Poisson" model, a log-linked linear model of the probability of COWO, which uses sandwich error estimation to produce robust standard errors (Zou 2004). All models of the independent effects of $PM_{2.5}$ exposures during preconception, the first, second, and third trimesters, whole pregnancy and the first 2 years of life (F2YL) were performed in 2 ways: with exposure as a categorical variable (quartiles) and as a continuous variable (scaled to IQR). For models of the joint effects of $PM_{2.5}$ exposure and MPBMI, $PM_{2.5}$ was binary, with high exposure defined as ≥ median exposure for the exposure period, and MPBMI was a 3-level categorical variable with normal-weight mothers as the reference group. Two product interaction terms, for the interaction of $PM_{2.5}$ with maternal overweight and for the interaction of $PM_{2.5}$ with maternal obesity, were used to evaluate interaction on the multiplicative scale; joint significance of both interaction terms was determined by Wald test. In addition, additivity of effects was evaluated by modeling the relative risk due to interaction (RERI) using the MOVER method (Zou 2008) . A RERI of 0 indicates no interaction. We adjusted for the following potential confounders known to be associated with childhood weight gain: maternal age at delivery, race/ethnicity, educational attainment, smoking status during pregnancy, diabetes, marital

status, household income per year, MPBMI, season of delivery, preterm birth, birth weight, and breastfeeding. All covariates were categorical and values were grouped according to the categories presented in Table 1; missing data for each covariate treated as a separate category. Due to the low rate of exclusive breastfeeding in the study population (5.0%), breastfeeding was treated as a dichotomous variable indicating any breastmilk; thus the breastfed group predominantly comprises children with a mixed diet of both breastmilk and formula. We did not include child age and sex in the final regression models because the BMI z-score was age- and sex-specific.

In addition, we examined the possibility of a non-linear relationship between $PM_{2.5}$ exposure and risk of COWO non-parametrically with restricted cubic splines (Durrleman and Simon 1989). Tests for non-linearity used the likelihood ratio test, comparing the model with only the linear term to the model with the linear and the cubic spline terms (Li et al. 2011). We also conducted the following sensitivity analyses to ensure the robustness of the results: individual and joint effects of $PM_{2.5}$ and MPBMI on COWO stratified by child's age, by warm and cold season, or within subgroups living within 10 km or 5 km distance of a monitor.

All tests were two-sided and $p<0.05$ was considered to be significant. All statistical analyses were performed using SAS 9.4 (SAS Institute Inc., Cary, NC, USA.). Figures were drawn with SAS 9.4 and Sigmaplot for windows version 12.5 (Build 12.5.0.38, Copyright©2011 Systat Software, Inc.).

Results

Population Characteristics

The prevalence of COWO in 1,446 children in the study population was 42.46% (41.36% for boys and 43.57% for girls). The mean age of assessment of COWO (i.e. the last well-child visit on record) was 6.70 years (median: 7.10 years). Among mothers, 54.56% of were overweight or obese before pregnancy (30.01% overweight and 24.55% obese). More than 90% of the subjects were

within 12 km of a monitor. A majority (66.25%) of the women in the study were African/African American and 28.49% were college graduates or above. The prevalence of maternal diabetes mellitus (DM) including type 1, type 2 or gestational DM was 9.96% (5.33% for type 1 or type 2 DM, 4.63% for gestational DM). Breastfeeding was practiced by 63.37% of the mothers.

When comparing population characteristics by COWO status (Table 1), mothers of COWO children were more likely to be older at delivery, be overweight or obese, have gestational diabetes and be African/African American. Children with COWO, compared to those without, tended to have higher birth weights and were less likely to be classified as low birth weight.

Ambient $PM_{2.5}$ exposures in the study population peaked in 2002 then decreased slightly over the remainder of study period (Figure S2). Individual exposures during different prenatal and postnatal periods studied were correlated (Spearman ρ: 0.35-0.89) (Table S1). The highest correlations were between the period of the whole pregnancy and trimester 1, trimester 3, and F2YL (Spearman ρ = 0.86, 0.85, 0.89, respectively). Of the total variability in exposures among subjects, 7.27% was attributable to monitor site and 92.73% was attributable to variability within subjects assigned to the same monitor (i.e. differences in dates of exposure).

Individual Association between MPBMI and COWO or Childhood BMI Z-score

The risk of COWO was significantly increased in overweight (RR=1.3[95% CI: 1.2, 1.6]) and obese (RR=1.6 [95% CI: 1.3, 1.8]) mothers' children compared to the risk of COWO in children of normal-weight mothers after adjusting for maternal age at delivery, race/ethnicity, education level, smoking status, diabetes, marital status, household income per year, season of the delivery, preterm birth, birth weight of baby and infants breast feeding (Table 2). In addition, when the relationship between COWO and MPBMI was assessed as a continuous variable, the risk of COWO increased significantly by 30% with each unit increase in MPBMI (RR=1.3[95% CI: 1.1, 1.4]. In additional analyses, childhood BMI-z was also positively associated with MPBMI (Table S2).

Individual Association between $PM_{2.5}$ Exposure and COWO or Childhood BMI z-Score

Compared to the lowest quartile of $PM_{2.5}$, the third and fourth quartiles of prenatal or postnatal $PM_{2.5}$ exposures were significantly associated with increased risk of COWO in all of the 6 exposure periods (with the exception of the RR for the fourth quartile in the first trimester and the third quartile in the second trimester [p=0.065 for both]) after adjusting for above-mentioned potential confounders (Table 2). The effect estimates were similar across the six exposure periods. In addition, risk of COWO was significantly increased for each IQR increase in with maternal ambient $PM_{2.5}$ exposure in the 5 exposure periods excluding preconception (RR=1.1 [95% CI: 1.0, 1.2] for the 1st trimester, 1.1[1.0, 1.2] for the 2nd trimester, 1.1 [1.0, 1.2] for the 3rd trimester, 1.1[1.0, 1.2] for the entire period of pregnancy and 1.1[1.0,1.2] for the first 2 years of life). Based on multivariable spline regression models, the risk ratio increased monotonically following a threshold with increasing of $PM_{2.5}$ in an exposure-response relationship pattern at each exposure period examined (Figure 1). Based on the modeled exposure-response curves, the effect of $PM_{2.5}$ exposure on COWO was strongest during the 2nd trimester compared to other periods of exposure. BMI-z score as a continuous outcome was also significantly increased when comparing the highest and lowest quartiles of $PM_{2.5}$ exposure in all exposure periods except the 1st trimester, for which the relationship was positive, but not statistically significant (Table S2).

In sensitivity analyses, estimated associations between the risk of COWO or childhood BMI z-score and ambient $PM_{2.5}$ exposure remained positive but were not significant with stratification by age group (Table S3). Associations remained positive with stratification by cool or warm season, but were slightly higher in the warm season and remained significant for the fourth quartile in some but not all exposure periods (Table S4). Findings were consistent with the main results when the analysis was limited to participants within 10 km or 5 km of a monitor (Tables S5 and S6).

Joint Associations between $PM_{2.5}$ Exposure and MPBMI on COWO or BMI Z-score

The risk of both COWO and childhood BMI z-score were significantly increased with maternal

overweight or obesity and exposure to ambient $PM_{2.5}$ during all exposure periods examined (Tables 3 and S7, Figure 2). The highest effects (RR ≥ 2.0) were observed among children whose exposure to $PM_{2.5}$ was in the high category ($PM_{2.5}$ ≥ median) and whose mothers were obese at the time of conception. Among mothers who were obese at conception (MPBMI≥30), the risk of COWO rose 11%-35% (depending on the exposure period) comparing those with high $PM_{2.5}$ (≥ median) to those with low $PM_{2.5}$ exposure (< median) in the same MPBMI stratum. Product interaction terms were not significant. RERI estimates for joint effects of high $PM_{2.5}$ exposure and MPBMI≥30 on COWO exceeded 0 for all exposure periods except the 3rd trimester; however, the 95% CIs all included 0; thus RERI was not significant for any time period.

Results of the evaluation of the joint effects of $PM_{2.5}$ and MPBMI on COWO and BMI-Z by stratified analysis were robust to additional stratification by age group, cool and warm season and distance from a monitor in sensitivity analyses (Table S8, Table S9, Table S10 and Table S11).

Discussion

To the best of our knowledge, this is the first report to examine the joint effects of MPBMI and ambient $PM_{2.5}$ exposure during periods of pregnancy and the first 2 years of life on COWO or childhood BMI-z. Our findings suggest $PM_{2.5}$ prenatal exposure and the first 2 years of life is an independent risk factor for COWO. Although in the present study interactions and RERI were not significant, children of mothers who were obese at the time of conception and who were in the upper 50^{th} percentile of exposure during prenatal and postnatal periods were at least twice as likely to be overweight or obese between ages 2 and 9 compared to children of mothers with MPBMI in the normal range and with $PM_{2.5}$ exposure below the 50^{th} percentile.

Interaction on the multiplicative scale was not observed in any periods of exposure examined. Furthermore, we found no quantitative evidence of supra-additivity since the 95% CIs for the relative excess risk due to interaction (RERI) included 0 for every exposure period (Table 3). However,

$PM_{2.5}$ exposure ≥ the period-specific median was associated with increased risk of COWO in all MPBMI strata. These findings suggest that reduction of $PM_{2.5}$ exposure may reduce risk of COWO in children of mothers with MPBMI in the normal, overweight, or obese ranges. Although our findings do not show that MPBMI modifies the relationship between $PM_{2.5}$ and COWO, children of mothers with obesity at the time of conception who were also exposed to $PM_{2.5}$ concentrations above the median of 10.46 – 10.89 $\mu g/m^3$ were at higher risk of COWO compared to children of mothers with one of these risk factors alone. Given the high prevalence of obesity among women of reproductive age in the U.S. and other developed countries (>30%) (Ogden et al. 2014; WHO 2013) and associated risk of COWO to their offspring, reduction of $PM_{2.5}$ exposure during the prenatal and postnatal period may be an important consideration in reducing COWO in this high-risk subpopulation.

Comparison across studies of air pollution and adiposity in children is complicated by the differences in study design and exact air pollutants and outcomes examined, but consistent with our findings, a body of literature suggests that exposure to air pollutants may contribute to increased adiposity early in life and these effects persist with age. A significant association between particulate matter ≤ 10 μm in diameter (PM_{10}) and COWO was reported in a large multi-city cross-sectional study of children age 2-14 years living in China between 2006 and 2008 (Dong et al. 2014). In a cohort of 3,318 children in California followed up throughout late childhood and adolescence, those living closest to roadways at age 10 had a significantly higher BMI at age 18 compared with children living further from roadways, and the effect increased synergistically with joint exposure to roadway pollution and secondhand tobacco smoke (Jerrett et al. 2010; McConnell et al. 2015).

The effects of prenatal exposure to $PM_{2.5}$ on birth outcomes has been studied extensively (Shah et al. 2011; Wang et al. 1997; Xu et al. 1995), but studies of postnatal outcomes are less common. In a study of the effect of prenatal exposure to air pollution on adiposity, Fleisch *et al* report that the highest quartile of neighborhood traffic density significantly associated with an increase in

weight-for-length gain (β=0.25 units, 95% CI: 0.01, 0.49), and higher odds of ≥95% weight-for-length (OR=1.84, 95% CI: 1.11, 3.05) at age 6 months (Fleisch et al. 2015). In the same study, $PM_{2.5}$ exposure was also positively associated with these two outcomes, but the association did not reach significance. In a follow up study of cardiometabolic health indicators in the same cohort, distance to a major roadway at the time of birth was inversely associated with BMI-z in early and mid-childhood; no association was found prenatal $PM_{2.5}$ exposure and BMI-z in early and mid-childhood. Prenatal exposure to polycyclic aromatic hydrocarbons (PAHs) during pregnancy was strongly associated with obesity at ages 5 (RR=1.79 [95% CI: 1.09, 2.96], N=422) and 7 (RR=2.26 [95% CI: 1.28, 4.00], N=341) years, in a study population demographically very similar to ours (Rundle et al. 2012), though unlike $PM_{2.5}$, PAHs are thought to act primarily via a hormonal mechanistic pathway.

The mechanism by which $PM_{2.5}$ impacts overweight and obesity is not well understood, but studies conducted in rodents show that $PM_{2.5}$ induces inflammatory responses in visceral adipose tissue (de Melo et al. 2015; Sun et al. 2009; Xu et al. 2010). Another rodent study reported increased inflammation of the epididymal fat pad in both dams and offspring exposed to unfiltered polluted air in Beijing during pregnancy compared with those exposed to filtered air suggesting a proinflammatory mechanistic pathway may underlie associations between maternal air pollution exposure and risk of COWO in offspring (Wei et al. 2016). Of note, the second trimester is a critical period of development of white adipose tissue (Gesta et al. 2007).

The main strength of this study is the prospective design and follow up of our study population from birth through childhood, which facilitated examination of the long-term effects of early life exposures to $PM_{2.5}$ and maternal overweight or obesity on adiposity in childhood. In addition, the use of medical records, structured questionnaires and quality assurance protocols, such as the clinical protocol for collection of child height and weight data, ensured high quality exposure, outcome, and covariate data. Postnatal confounding variables controlled for in the study included breastfeeding and

age and sex, the last two being controlled by the use of age and sex-specific BMI-z scores. However, there may be residual confounding from prenatal and postnatal variables not accounted for in the model.

Moderate to strong correlations between exposures during different prenatal and postnatal periods limited our ability to examine the effects of a specific period of exposure while controlling for exposure during other periods. To avoid collinearity, we examined each exposure period in a separate single-period model. Period-specific risk ratios may reflect the effects of chronic exposure or exposure during other prenatal or postnatal periods.

Restriction of our study to a single city limits the generalizability of our findings to other geographic locations or to other populations with a different social and demographic make-ups. Generalizability may also be limited by the high prevalences of preterm birth and low birth weight in the BBC compared to the general population, as low birth weight is a risk factor for COWO (Reilly et al. 2005). That said, the observation of an effect of $PM_{2.5}$ on COWO at relatively low exposures (near or below current EPA daily $PM_{2.5}$ standard equal to 12 $\mu g/m^3$) suggests that populations at similar or higher exposures may also be at risk. $PM_{2.5}$ concentrations in Boston are highest in summer reflecting the high contribution of regional air pollution to $PM_{2.5}$ concentrations in the area. A study of $PM_{2.5}$ composition in Boston conducted between 2002 and 2010 found that regional air pollution sources account for almost half of $PM_{2.5}$ pollution in Boston (48%) followed by motor vehicles (21%), and wood burning (19%) as the highest contributing sources, underscoring the public health importance of decreases in both regional and traffic-related pollution (Masri et al. 2014).

Another limitation is that our exposure assessment may not fully account for spatial variability in ambient $PM_{2.5}$ concentrations within the area around each stationary monitor, resulting in some exposure misclassification, which might lead us to underestimate the risk of exposure on COWO. However, more than 85% of our population lived within 10 km of a monitor a distance within which $PM_{2.5}$ concentrations are relatively homogeneous (Kloog et al. 2012). Furthermore, our results were

robust in subgroup analysis of subjects within 10 km and 5 km of a monitor, supporting the characterization of exposure in our study by stationary $PM_{2.5}$ monitors.

Conclusion

This is the first longitudinal birth cohort study, to the best of our knowledge, to examine the joint effects of MPBMI and early-life ambient $PM_{2.5}$ exposure on the risk of childhood overweight or obesity (COWO). We report a positive monotonic relationship between ambient $PM_{2.5}$ exposure in-utero and birth to 2 years of life and risk of COWO. Furthermore, children of mothers who are obese at conception and who are exposed to $PM_{2.5}$ at or above 10.5 – 10.9 $\mu g/m^3$ are at least twice or more the risk of COWO compared to children of mothers with MPBMI in the normal range and low $PM_{2.5}$ exposure. These findings have implications for air pollution policies given a significant effect among participants exposed at near or below the federal $PM_{2.5}$ annual standard of 12 $\mu g/m^3$ (U.S. EPA 2013).

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Table 1. Characteristics of mother-infant pairs of the participants. *

Variables	Children without COWO (n=832)	Children with COWO (n=614)	*P*
Maternal Age at delivery, years	27.4(22.7,32.7)	28.8(24.0,34.0)	0.001
Maternal Pre-pregnancy Body mass index, kg/m^2			<0.001
Normal weight (18.5-24.9)	439(52.8)	218(35.5)	
Overweight (25.0-29.9)	232(27.9)	202(32.9)	
Obesity (>=30.0)	161(19.4)	194(31.6)	
Maternal Race/Ethnic, # (%)			0.523
Hispanic	146(17.5)	106(17.3)	
White	49(5.9)	30(4.9)	
African/African American	533(64.1)	425(69.2)	
Others	102(12.3)	53(8.6)	
Missing	2(0.2)	0(0.0)	
Maternal Education category, # (%)			0.718
Middle school or below	287(34.5)	211(34.4)	
High school	307(36.9)	213(34.7)	
College or above	230(27.6)	182(29.6)	
Missing	8(1.0)	8(1.3)	
Married (mother), # (%)	556(66.8)	402(65.5)	0.837
Continue smoking during pregnancy (mother), # (%)	87(10.5)	73(11.9)	0.792
Gestational Diabetes Mellitus, # (%)	30(3.6)	37(6.0)	0.002
Born in USA (mother), # (%)	354(42.5)	230(37.5)	0.141
Parity, # (%)			0.808
0	350(42.1)	251(40.9)	
1+	481(57.8)	363(59.1)	
Missing	1(0.1)	0(0.0)	
Season at delivery, # (%)			0.485
Spring (Mar. to May)	194(23.3)	124(20.2)	
Summer (June to Aug.)	210(25.2)	164(26.7)	
Autumn (Sept. to Nov.)	220(26.4)	160(26.1)	
Winter (Dec. to Feb.)	208(25.0)	166(27.0)	
Low birth weight (birth weight<2500g)	263(31.6)	133(21.7)	<0.001
Preterm**, # (%)	251(30.2)	163(26.5)	0.132
Gestational age, weeks	38.6(36.3,39.9)	38.9(36.7,40.0)	0.030
Birth weight, g	2925.0(2357.5,3350.0)	3152.5(2595.0,3595.0)	<0.001
Age of child at last follow-up			
Median(Q1,Q3)	6.6(4.0,8.9)	7.7(5.4,9.2)	<0.001
Mean±SD	6.3±2.5	7.2±2.2	<0.001
Boys (child), # (%)	408(49.0)	315(51.3)	0.395
Breast feeding	546(65.6)	380(61.9)	0.104

* COWO is defined as childhood overweight or obesity. Underweight, normal weight, overweight and obesity are defined as maternal BMI<18.5 kg/m2, between 18.5 and 24.9 kg/m2, between 25 and 29.9 kg/m2 and equal to or more than 30 kg/m2, respectively.

** Preterm is defined as gestational age<37 weeks.

Continuous data is described as median (1st quartile [Q1], 3rd quartile [Q3]) and Mann-Whitney U test is applied to compare the difference between two groups because their distribution is skewed.

Table 2. Individual effects of maternal pre-pregnancy BMI or ambient $PM_{2.5}$ exposure on the risk of childhood overweight or obesity.

Variables	n	COWO #(%)	*Crude*		*Adjusted*	
			RR(95% CI)	*P*	*RR(95% CI)*	*P*
Maternal BMI, Kg/m^2 *						
18.5-24.9 (Normal weight)	657	218(33.2)	Ref.	Ref.	Ref.	Ref.
25.0-29.9 (Overweight)	434	202(46.5)	1.4(1.2,1.6)	<0.001	1.3(1.2,1.6)	<0.001
≥30.0 (Obesity)	355	194(54.6)	1.6(1.4,1.9)	<0.001	1.6(1.3,1.8)	<0.001
Per kg/m^2	.		1.3(1.2,1.4)	<0.001	1.3(1.1,1.4)	<0.001
Ambient $PM_{2.5}$, $\mu g/m^3$						
Preconception						
Q1 (4.48-8.85)	348	130(37.4)	Ref.	Ref.	Ref.	Ref.
Q2 (8.86-10.59)	350	138(39.4)	1.1(0.9,1.3)	0.574	1.1(0.9,1.3)	0.420
Q3 (10.59-12.36)	348	155(44.5)	1.2(1.0,1.4)	0.055	1.2(1.0,1.4)	0.037
Q4 (>12.36)	348	163(46.8)	1.3(1.1,1.5)	0.012	1.3(1.1,1.5)	0.011
Per IQR=3.49 $\mu g/m^3$			1.1(1.0,1.2)	0.110	1.1(1.0,1.2)	0.134
1st trimester	.					
Q1 (4.16-8.73)	353	136(38.5)	Ref.	Ref.	Ref.	Ref.
Q2 (8.74-10.58)	353	130(36.8)	1.0(0.8,1.2)	0.641	1.0(0.8,1.1)	0.597
Q3 (10.59-12.28)	353	169(47.9)	1.2(1.0,1.5)	0.013	1.2(1.0,1.4)	0.021
Q4 (>12.28)	354	161(45.5)	1.2(1.0,1.4)	0.062	1.2(1.0,1.4)	0.065
Per IQR=3.58 $\mu g/m^3$			1.1(1.0,1.2)	0.025	1.1(1.0,1.2)	0.025
2nd trimester						
Q1 (5.39-8.79)	357	143(40.1)	Ref.	Ref.	Ref.	Ref.
Q2 (8.80-10.54)	358	123(34.4)	0.9(0.7,1.0)	0.116	0.9(0.7,1.0)	0.113
Q3 (10.55-12.22)	356	168(47.2)	1.2(1.0,1.4)	0.056	1.2(1.0,1.4)	0.065
Q4 (>12.22)	358	172(48.0)	1.2(1.0,1.4)	0.032	1.2(1.0,1.4)	0.037
Per IQR=3.42 $\mu g/m^3$			1.1(1.0,1.2)	0.023	1.1(1.0,1.2)	0.035
3rd trimester	.					
Q1 (3.78-8.64)	354	131(37.0)	Ref.	Ref.	Ref.	Ref.
Q2 (8.65-10.52)	355	137(38.6)	1.0(0.9,1.3)	0.663	1.0(0.9,1.3)	0.607
Q3 (10.53-12.32)	355	164(46.2)	1.2(1.0,1.5)	0.014	1.2(1.0,1.5)	0.012
Q4 (>12.32)	354	177(50.0)	1.4(1.1,1.6)	0.001	1.3(1.1,1.6)	0.001
Per IQR=3.64 $\mu g/m^3$			1.1(1.0,1.2)	0.030	1.1(1.0,1.2)	0.042
Whole pregnancy						
Q1 (5.88-8.80)	361	136(37.7)	Ref.	Ref.	Ref.	Ref.
Q2 (8.81-10.66)	362	139(38.4)	1.0(0.8,1.2)	0.841	1.0(0.9,1.2)	0.740
Q3 (10.67-11.93)	362	161(44.5)	1.2(1.0,1.4)	0.064	1.2(1.0,1.4)	0.050
Q4 (>11.93)	361	178(49.3)	1.3(1.1,1.5)	0.002	1.3(1.1,1.5)	0.002
Per IQR=3.17 $\mu g/m^3$			1.1(1.0,1.2)	0.017	1.1(1.0,1.2)	0.041
The first 2 years of life	.					
Q1 (6.13-9.06)	361	136(37.7)	Ref.	Ref.	Ref.	Ref.
Q2 (9.07-10.21)	362	135(37.3)	1.0(0.8,1.2)	0.916	1.0(0.8,1.2)	0.994
Q3 (10.22-11.99)	362	165(45.6)	1.2(1.0,1.4)	0.032	1.3(1.1,1.5)	0.010
Q4 (>11.99)	361	178(49.3)	1.3(1.1,1.5)	0.002	1.3(1.1,1.5)	0.002
Per IQR=3.01 $\mu g/m^3$			1.1(1.0,1.2)	0.015	1.1(1.0,1.2)	0.038

Adjusted for maternal age at delivery, race/ethnicity, education level, smoking status, marriage status, pre-pregnancy BMI, diabetes, annual household income, season of the delivery, preterm birth, birth weight of baby and infant breast feeding. IQR indicates the interquartile range.

* Not adjusted for mother's pre-pregnancy BMI and mother's BMI<18.5 kg/m^2 excluded.

Table 3. The joint effects of maternal pre-pregnancy BMI and $PM_{2.5}$ exposure on the risk of childhood overweight or obesity.

Maternal BMI	$PM_{2.5}$ μg/m^3 ≤	*n*	*COWO #(%)*	*Crude*		*Adjusted*	
				RR(95% CI)	*p*	*RR(95% CI)*	*p*
Preconception	≥10.80						
Normal weight	No	325	85(26.2)	1.0(1.0,1.0)	Ref.	1.0(1.0,1.0)	Ref.
Normal weight	Yes	312	124(39.7)	1.5(1.2,1.9)	<0.001	1.5(1.2,1.9)	<0.001
Overweight	No	203	99(48.8)	1.9(1.5,2.3)	<0.001	1.8(1.5,2.3)	<0.001
Overweight	Yes	215	91(42.3)	1.6(1.3,2.1)	<0.001	1.5(1.2,1.9)	0.001
Obesity	No	170	84(49.4)	1.9(1.5,2.4)	<0.001	1.7(1.4,2.2)	<0.001
Obesity	Yes	169	103(60.9)	2.3(1.9,2.9)	<0.001	2.3(1.8,2.8)	<0.001
Interaction $PM_{2.5}$*Overweight				0.6(0.4,0.8)	0.006	0.6(0.4,0.8)	0.004
Interaction $PM_{2.5}$*Obesity				0.8(0.5,1.2)	0.305	0.9(0.6,1.3)	0.479
Interaction $PM_{2.5}$*Overweight+Obesity*				1.1(0.7,1.5)	0.769	1.1(0.8,1.6)	0.498
$RERI_{overweight}$ (95% CI) = -0.44(-1.52,-0.19)							
$RERI_{obesity}$ (95% CI) = 0.04(-0.52,0.31)							
1st trimester	≥10.81	.					
Normal weight	No	332	91(27.4)	1.0(1.0,1.0)	Ref.	1.0(1.0,1.0)	Ref.
Normal weight	Yes	313	122(39.0)	1.4(1.1,1.8)	0.002	1.4(1.1,1.7)	0.005
Overweight	No	198	88(44.4)	1.6(1.3,2.0)	<0.001	1.5(1.2,1.9)	<0.001
Overweight	Yes	225	105(46.7)	1.7(1.4,2.1)	<0.001	1.6(1.3,2.0)	<0.001
Obesity	No	176	87(49.4)	1.8(1.4,2.3)	<0.001	1.7(1.3,2.1)	<0.001
Obesity	Yes	169	103(60.9)	2.2(1.8,2.8)	<0.001	2.1(1.7,2.6)	<0.001
Interaction $PM_{2.5}$*Overweight				0.7(0.5,1.1)	0.130	0.8(0.5,1.2)	0.214
Interaction $PM_{2.5}$*Obesity				0.9(0.6,1.3)	0.478	0.9(0.6,1.3)	0.602
Interaction $PM_{2.5}$*Overweight+Obesity*				1.0(0.7,1.4)	0.941	1.0(0.7,1.4)	0.953
$RERI_{overweight}$ (95% CI) = -0.11(-0.70,0.06)							
$RERI_{obesity}$ (95% CI) = 0.03(-0.49,0.25)							
2nd trimester	≥10.75	.					
Normal weight	No	330	84(25.5)	1.0(1.0,1.0)	Ref.	1.0(1.0,1.0)	Ref.
Normal weight	Yes	320	132(41.3)	1.6(1.3,2.0)	<0.001	1.6(1.2,2.0)	<0.001
Overweight	No	205	94(45.9)	1.8(1.4,2.3)	<0.001	1.7(1.3,2.2)	<0.001
Overweight	Yes	225	104(46.2)	1.8(1.4,2.3)	<0.001	1.7(1.3,2.2)	<0.001
Obesity	No	180	88(48.9)	1.9(1.5,2.4)	<0.001	1.8(1.4,2.2)	<0.001
Obesity	Yes	169	104(61.5)	2.4(1.9,3.0)	<0.001	2.3(1.8,2.9)	<0.001
Interaction $PM_{2.5}$*Overweight				0.6(0.4,0.9)	0.017	0.6(0.4,1.0)	0.032
Interaction $PM_{2.5}$*Obesity				0.8(0.5,1.2)	0.209	0.8(0.6,1.2)	0.389
Interaction $PM_{2.5}$*Overweight+Obesity*				1.0(0.7,1.4)	0.849	1.0(0.7,1.5)	0.870
$RERI_{overweight}$ (95% CI) = -0.23(-1.00,0.00)							
$RERI_{obesity}$ (95% CI) = 0.04(-0.54,0.34)							
3rd trimester	≥10.75	.					
Normal weight	No	336	92(27.4)	1.0(1.0,1.0)	Ref.	1.0(1.0,1.0)	Ref.
Normal weight	Yes	315	126(40.0)	1.5(1.2,1.8)	0.001	1.4(1.1,1.8)	0.001
Overweight	No	198	86(43.4)	1.6(1.3,2.0)	<0.001	1.5(1.2,1.9)	0.001
Overweight	Yes	225	114(50.7)	1.9(1.5,2.3)	<0.001	1.8(1.4,2.2)	<0.001
Obesity	No	175	90(51.4)	1.9(1.5,2.4)	<0.001	1.8(1.4,2.2)	<0.001
Obesity	Yes	169	101(59.8)	2.2(1.8,2.7)	<0.001	2.0(1.6,2.5)	<0.001
Interaction $PM_{2.5}$*Overweight				0.8(0.5,1.2)	0.256	0.8(0.6,1.2)	0.338
Interaction $PM_{2.5}$*Obesity				0.8(0.5,1.2)	0.251	0.8(0.5,1.2)	0.301
Interaction $PM_{2.5}$*Overweight+Obesity*				0.9(0.6,1.2)	0.433	0.9(0.6,1.3)	0.496
$RERI_{overweight}$ (95% CI) = -0.04 (-0.55, 0.14)							
$RERI_{obesity}$ (95% CI) = -0.04 (-0.64, 0.20)							
Whole pregnancy	≥10.89	.					
Normal weight	No	335	93(27.8)	1.0(1.0,1.0)	Ref.	1.0(1.0,1.0)	Ref.
Normal weight	Yes	322	125(38.8)	1.4(1.1,1.7)	0.003	1.4(1.1,1.7)	0.007
Overweight	No	214	96(44.9)	1.6(1.3,2.0)	<0.001	1.5(1.2,1.9)	<0.001
Overweight	Yes	220	106(48.2)	1.7(1.4,2.2)	<0.001	1.6(1.3,2.1)	<0.001
Obesity	No	174	86(49.4)	1.8(1.4,2.2)	<0.001	1.6(1.3,2.1)	<0.001
Obesity	Yes	181	108(59.7)	2.1(1.7,2.7)	<0.001	2.0(1.6,2.5)	<0.001

Maternal BMI	$PM_{2.5}$ $\mu g/m^3$	*n*	*COWO #(%)*	*Crude*		*Adjusted*	
				RR(95% CI)	*p*	*RR(95% CI)*	*p*
Interaction $PM_{2.5}$*Overweight				0.8(0.5,1.1)	0.179	0.8(0.5,1.2)	0.281
Interaction $PM_{2.5}$*Obesity				0.9(0.6,1.3)	0.460	0.9(0.6,1.4)	0.698
Interaction $PM_{2.5}$*Overweight+Obesity*				1.0(0.7,1.4)	0.885	1.0(0.7,1.5)	0.854
$RERI_{overweight}$ (95% CI) = -0.08 (-0.62, 0.09)							
$RERI_{obesity}$ (95% CI) = 0.04 (-0.46, 0.25)							
The first 2 years of life	≥10.46	.					
Normal weight	No	342	90(26.3)	1.0(1.0,1.0)	Ref.	1.0(1.0,1.0)	Ref.
Normal weight	Yes	315	128(40.6)	1.5(1.2,1.9)	<0.001	1.5(1.2,1.9)	<0.001
Overweight	No	207	97(46.9)	1.8(1.4,2.2)	<0.001	1.7(1.3,2.1)	<0.001
Overweight	Yes	227	105(46.3)	1.8(1.4,2.2)	<0.001	1.7(1.4,2.1)	<0.001
Obesity	No	174	84(48.3)	1.8(1.5,2.3)	<0.001	1.7(1.3,2.1)	<0.001
Obesity	Yes	181	110(60.8)	2.3(1.9,2.9)	<0.001	2.2(1.8,2.8)	<0.001
Interaction $PM_{2.5}$*Overweight				0.6(0.4,0.9)	0.023	0.7(0.5,1.0)	0.039
Interaction $PM_{2.5}$*Obesity				0.8(0.6,1.2)	0.307	0.9(0.6,1.3)	0.469
Interaction $PM_{2.5}$*Overweight+Obesity*				1.0(0.7,1.4)	0.988	1.0(0.7,1.5)	0.797
$RERI_{overweight}$ (95% CI) = -0.21 (-0.92, 0.01)							
$RERI_{obesity}$ (95% CI) = 0.04 (-0.48, 0.31)							

Normal weight, overweight and obesity are defined as maternal pre-pregnancy BMI: 18.5-24.9, 25.0-29.9 and >=30.0 kg/m^2, respectively.

Adjusted for maternal age at delivery, race/ethnicity, education level, smoking status, diabetes, marriage status, household income per year, season of the delivery, preterm birth, birth weight of baby and infants breast feeding. Mother's pre-pregnancy BMI<18.5 kg/m^2 was excluded.

RERI indicates the relative excess risk of childhood overweight/obesity due to interaction using MOVER method

* A Wald test was performed on the first two interaction terms to evaluate the interaction between $PM_{2.5}$ and Overweight+Obesity

Figure 1. Associations of early-life ambient $PM_{2.5}$ exposure with the risk of childhood overweight or obesity based on spline regression models. *All estimates are adjusted for maternal age at delivery, race/ethnicity, education level, smoking status, diabetes, marriage status, body mass index before pregnancy, household income per year, season of the delivery, preterm birth, breast feeding and birth weight of baby. COWO indicates childhood overweight/obesity.*

Figure 2. Adjusted combined effects of mother's pre-pregnancy BMI and exposure to $PM_{2.5}$ level on the risk of childhood overweight or obesity by time point (sorted by $PM_{2.5}$ level). *All estimates are adjusted for maternal age at delivery, race/ethnicity, education level, smoking status, diabetes, marriage status, household income per year, season of the delivery, preterm birth, breast feeding and birth weight of baby.* Normal, overweight, and obese categories indicate mother's pre-pregnancy BMI are 18.5-24.9, 25.0-29.9 and >=30 kg/m^2, respectively; Low indicates ambient $PM_{2.5}$<12μg/m^3; High indicates exposed to $PM_{2.5}$>=12 μg/m^3.

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Figure 1.

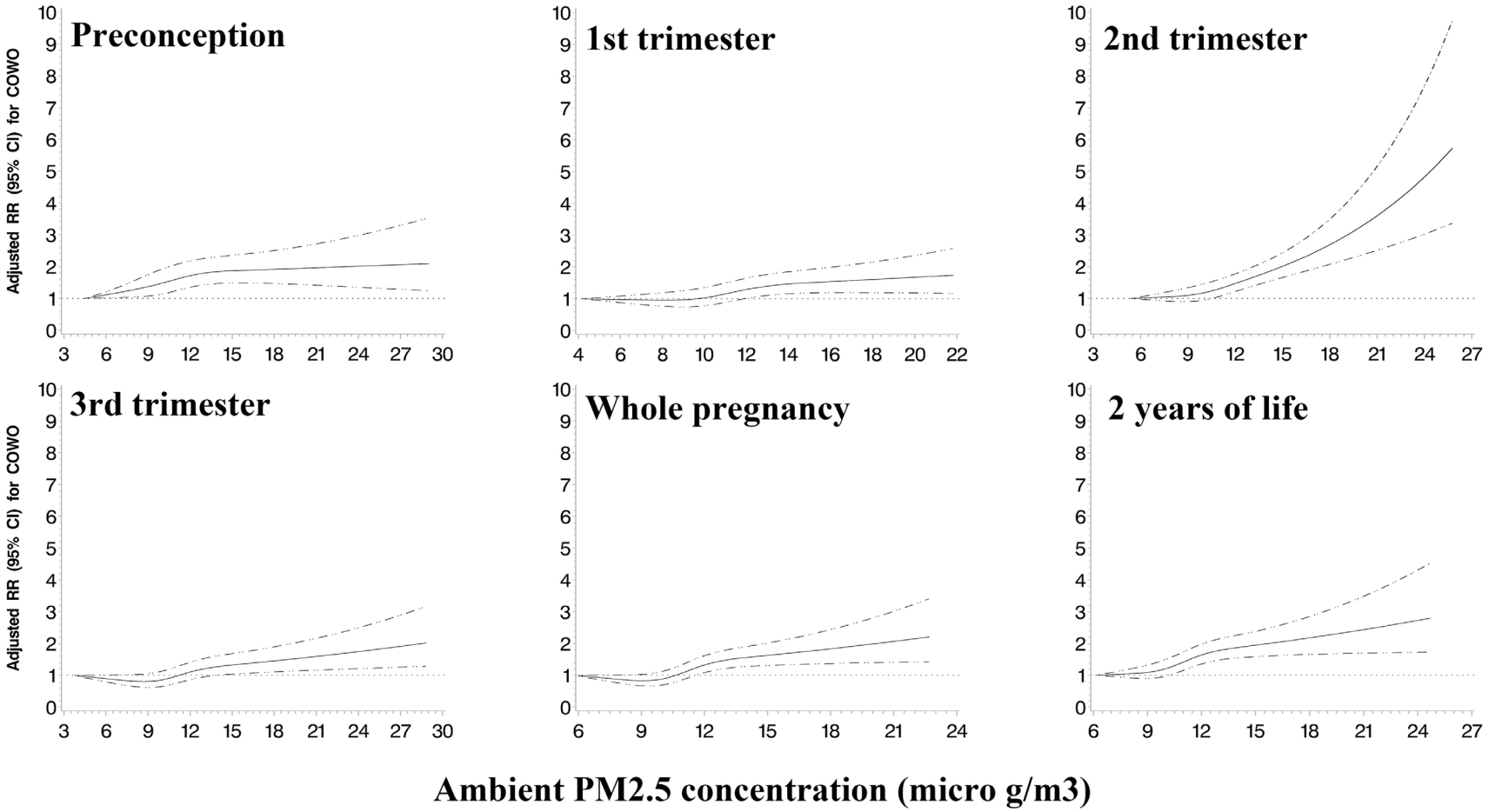
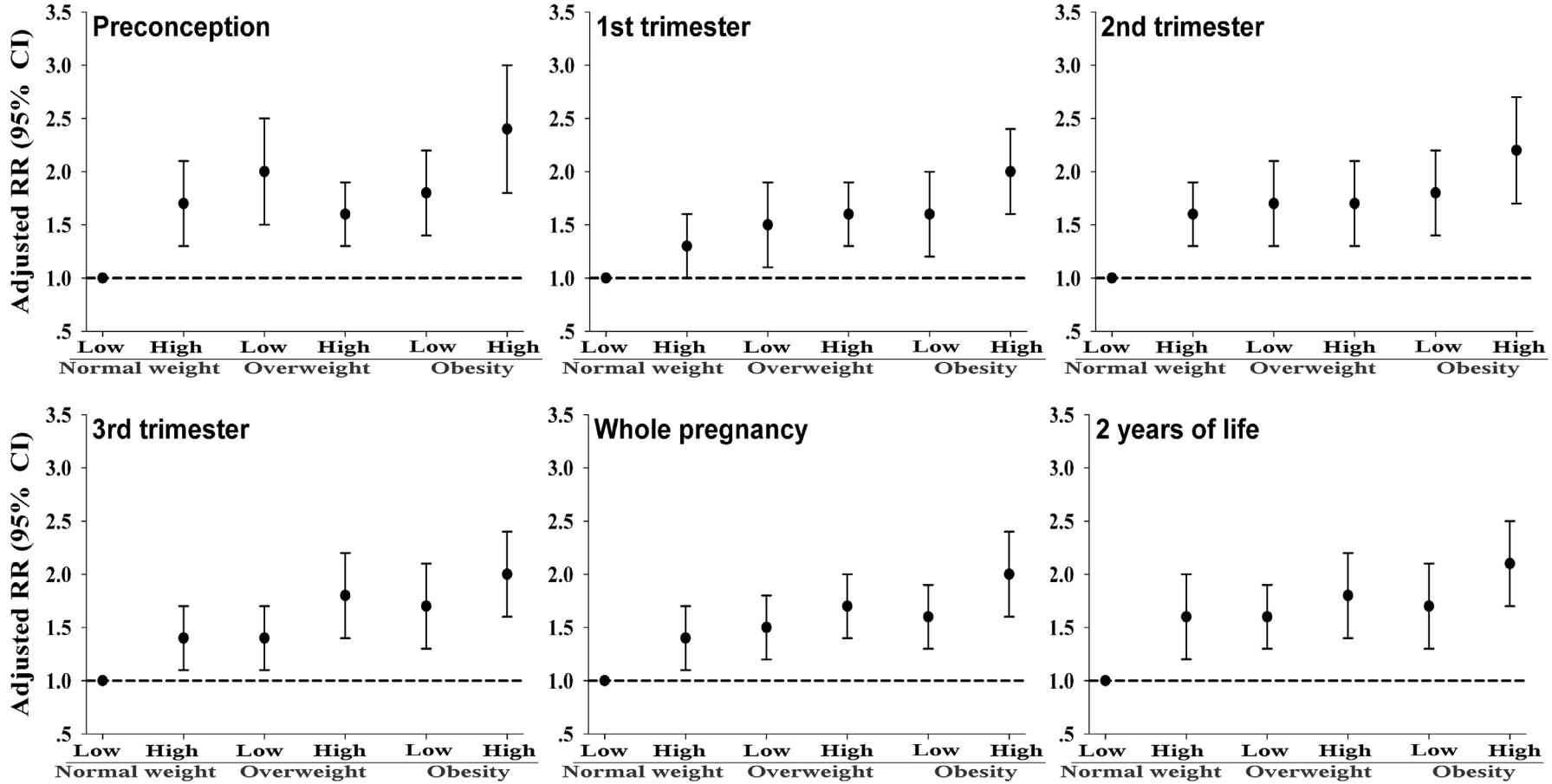


Figure 2.


Preconception
1st trimester
2nd trimester
3rd trimester
Whole pregnancy
2 years of life
Adjusted RR (95% CI)
3.5
3.0
2.5
2.0
1.5
1.0
.5
Low
High
Normal weight
Overweight
Obesity